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A NOVEL TARGET IN THE TREATMENT OF COLORECTAL CANCER; CRD-BP

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Abstract: Colorectal cancer is the third leading cause of cancer-related deaths in women in the United States and the second leading cause in men. It is expected to cause about 50,260 deaths during 2017. The choice of treatment of colorectal cancer depends mainly on the location of the tumor and the stage of the disease. Chemotherapy is used for advanced cancers. However activation of anti-apoptotic pathways and upregulation of multidrug resistance membrane transporters in advanced colorectal cancer cells render them resistant to drugs. Therefore, targeting factors regulating these mechanisms would sensitize colorectal cancer cells to treatment. Constitutive activation of the Wnt/β-catenin signaling pathway is one of the central drivers of the development of colorectal cancer. We previously showed that β-catenin stabilizes the mRNA encoding the F-box protein β-TrCP1, and identified the RNA-binding protein CRD-BP (coding region determinant-binding protein) as a previously unknown target of β-catenin/Tcf transcription factor. CRD-BP binds to the coding region of β-TrCP1 mRNA, stabilizes it and elevates its levels. This increase of β-TrCP1 levels results in the activation of the Skp1-Cullin1-F-box protein (SCF)(β-TrCP) E3 ubiquitin ligase and in accelerated turnover of its substrates. One of the major physiological outcomes of β-TrCP1 upregulation is the β-TrCP1-dependant activation of the NF-κB signaling pathway and suppression of apoptosis in colorectal cancer cells. CRD-BP also upregulates GLI1 and c-myc which promote cell proliferation and cell cycle progression. Moreover, CRD-BP was shown to induce the multidrug resistance-1 membrane transporter MDR-1 that contributes to drug efflux from the cells. Therefore, CRD-BP may promote the resistance of colorectal cancers to chemotherapeutics by contributing to both inhibition of apoptosis and active drug efflux from cells. CRD-BP is absent or scarce in adult tissues but re-activated and/or over-expressed in various tumors including primary colorectal cancers. Hence, its inhibition would have no or little effect on normal cells. This makes CRD-BP an attractive target to sensitize colorectal cancer cells to chemotherapeutics. Our hypothesis is that inhibiting CRD-BP can sensitize colorectal cancer cells to drugs. To test our hypothesis we used the colorectal cancer cells HCT116, RKO and the chemotherapeutic drug 5-Fluorouracil (5-FU). We assessed; 1) cell proliferation using the MTT assay, 2) apoptosis of the cells using caspase assay, and 3) cell senescence by using the β-galactosidase assay. We observed that CRD-BP inhibition significantly reduces the proliferation of HCT116 cells. This reduction was more pronounced when CRD-BP inhibition was combined with the drug treatment ($P<0.01$). This inhibition in cell proliferation was associated with a significant increase in apoptosis in the same cells ($P<0.001$). However, CRD-BP inhibition had no effect on the growth and proliferation of RKO cells. Our data suggest inhibition of CRD-BP potentiates the anti-growth effect of 5-FU in HCT116 cells which exhibit constitutive activation of the Wnt signaling by promoting apoptosis.

Key words: Colorectal cancer; CRD-BP; drug resistance; 5-FU.

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